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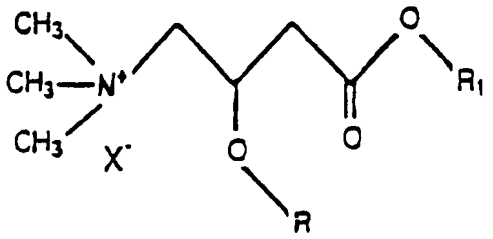
(54) Esters of L-carnitine and acyl L-carnitine endowed with muscle relaxant activityselective on gastrointestinal tract and pharmaceutical compositions containing same.

(57) Esters of L-carnitine and acyl L-carnitine of formula (I):



(I)

wherein
R is hydrogen or is a straight or branched, saturated or unsaturated acyl group having 2 to 26 carbon atoms;
R_1 is a straight or branched, saturated or unsaturated alkyl group having 4 to 26 carbon atoms; and
X^- is the anion of a pharmacologically acceptable acid
are endowed with potent muscle relaxant activity selective on the gastrointestinal tract and are therefore therapeutically useful for treating e.g. adaptive colitis syndromes.

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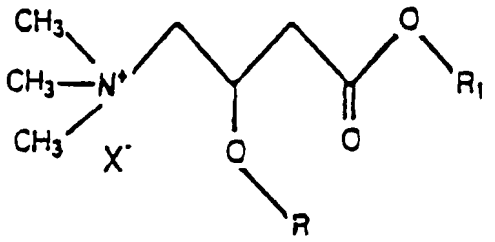
The present invention relates to esters of L-carnitine and acyl L-carnitine of formula (I):



(I)

wherein

R is hydrogen or is a straight or branched, saturated or unsaturated acyl group having 2 to 26 carbon atoms;

R_1 is a straight or branched, saturated or unsaturated alkyl group having 4 to 26 carbon atoms; and

X^- is the anion of a pharmacologically acceptable acid.

These compounds are endowed with calcium-antagonist activity. However, unlike known calcium antagonists (such as e.g. Diltiazem, Verapamil and Nitrendipina) it was surprisingly found that the compounds of formula (I) exhibit potent muscle relaxant activity affecting the gastrointestinal tract selectively, with no effect whatsoever on the cardiovascular tract. Moreover, they exhibit remarkable muscle relaxant activity on the intestinal contractility brought about by contracture-inducing drugs having different mode of action (e.g. acetylcholine).

The compounds of formula (I) are useful as active ingredients in orally or parenterally administrable pharmaceutical compositions, for treating adaptive colitis syndromes as well as all those pathologies wherein an increase of intestinal contractility and/or motility can be found.

In compounds of formula (I), when R is a straight saturated acyl group having 2 to 26 carbon atoms, it is preferably selected from acetyl, propionyl, butyryl, palmitoyl, undecanoyl and hexacosanoyl;

when R is branched acyl, it is preferably selected from isobutyryl, isovaleryl, isocaproyl and 2- methylhexanoyl;

when R is unsaturated acyl, it is preferably 10-undecenoyl.

As regards R_1 (alkyl group having 4 to 26 carbon atoms), when R_1 is straight saturated alkyl, it is preferably selected from n-butyl, n-heptyl, n-undecyl and n-hexacosyl;

when R_1 is branched alkyl, it is preferably selected from isobutyl, isooctyl, hexylmethylcarbyl, ethylpentylcarbyl, ethylhexylcarbyl, decylmethylcarbyl, dipentylcarbyl and methylnonylcarbyl;

when R_1 is unsaturated alkyl, it is preferably pentylvinylcarbyl or 10-undecenyl.

The anion X^- of the pharmacologically acceptable acid is preferably selected from chloride; bromide; iodide; aspartate, particularly acid aspartate; citrate, particularly acid citrate; tartrate; phosphate, particularly acid phosphate; fumarate, particularly acid fumarate; glycerophosphate; glucosephosphate; lactate; maleate, particularly acid maleate; orotate; oxalate, particularly acid oxalate; sulphate, particularly acid sulphate; trichloroacetate; trifluoroacetate and methansulphonate.

The esters of formula (I) may be prepared following two distinct synthesis processes. The first process (illustrated in the Synthesis Scheme 1) comprises the steps consisting of:

(a) halogenating an acyl L-carnitine with a halogenating agent such as thionyl chloride and oxalyl chloride (molar ratio comprised between 1:1 and 1:4) in an anhydrous organic inert solvent such as acetonitrile or methylene chloride at a temperature comprised between 0 °C and 30 °C for 1-4 hours, concentrating the raw reaction product and using it in the following step;

(b) dissolving the acid chloride of step (a) in an anhydrous organic inert solvent such as acetonitrile or methylene chloride and adding the alcohol diluted in the same solvent at a ratio comprised between 1:1 and 1:2 at temperatures comprised between 0 °C and 30 °C for 2-10 hours, concentrating the solution and, if needed, purifying the compound by chromatography on silica gel; and

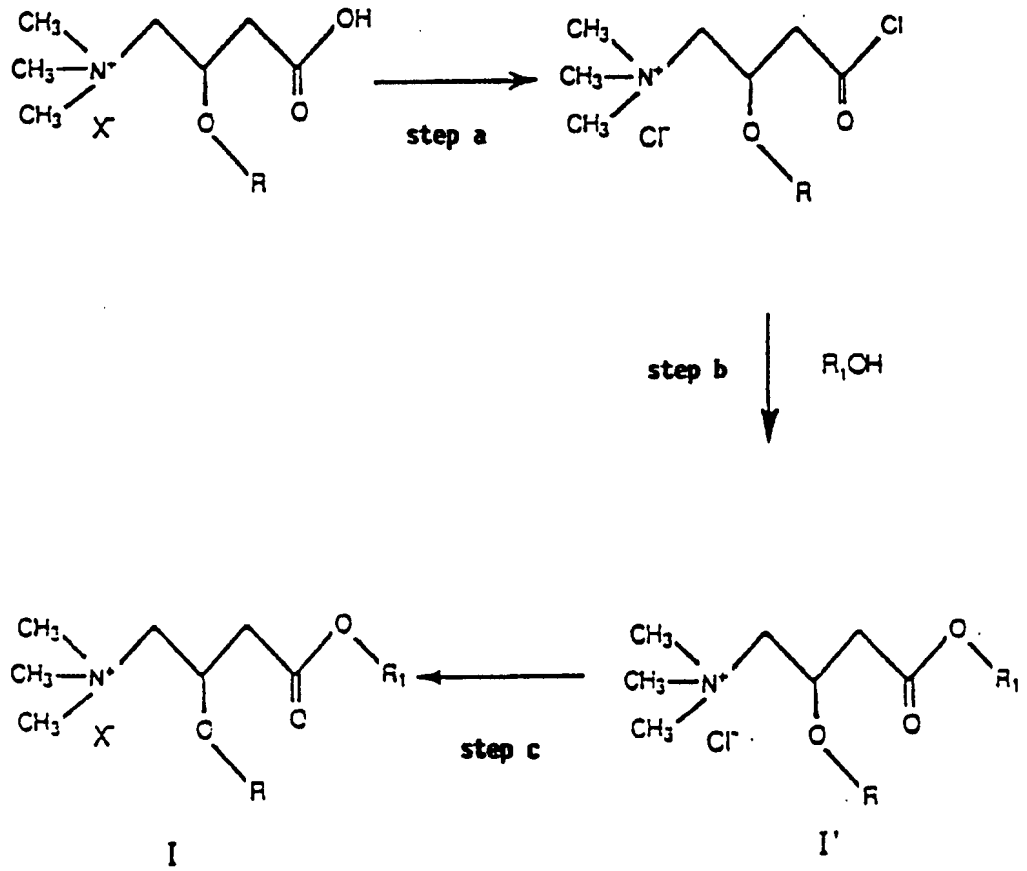
(c) eluting the product dissolved in water or in an organic solvent on a strongly basic ion exchange resin such as Amberlite IRA 402 or on a weakly basic ion exchange resin such as Amberlist A 21, activated with the desired HX acid and isolating the final product by lyophilization or concentration.

The second process (illustrated in the Synthesis Scheme 2) comprises the steps consisting of:

(a') reacting carnitine or an acyl carnitine inner salt with the relevant alkyl halogenide (preferably bromide or iodide) in an organic anhydrous inert solvent at a temperature comprised between 30 °C and 60 °C for

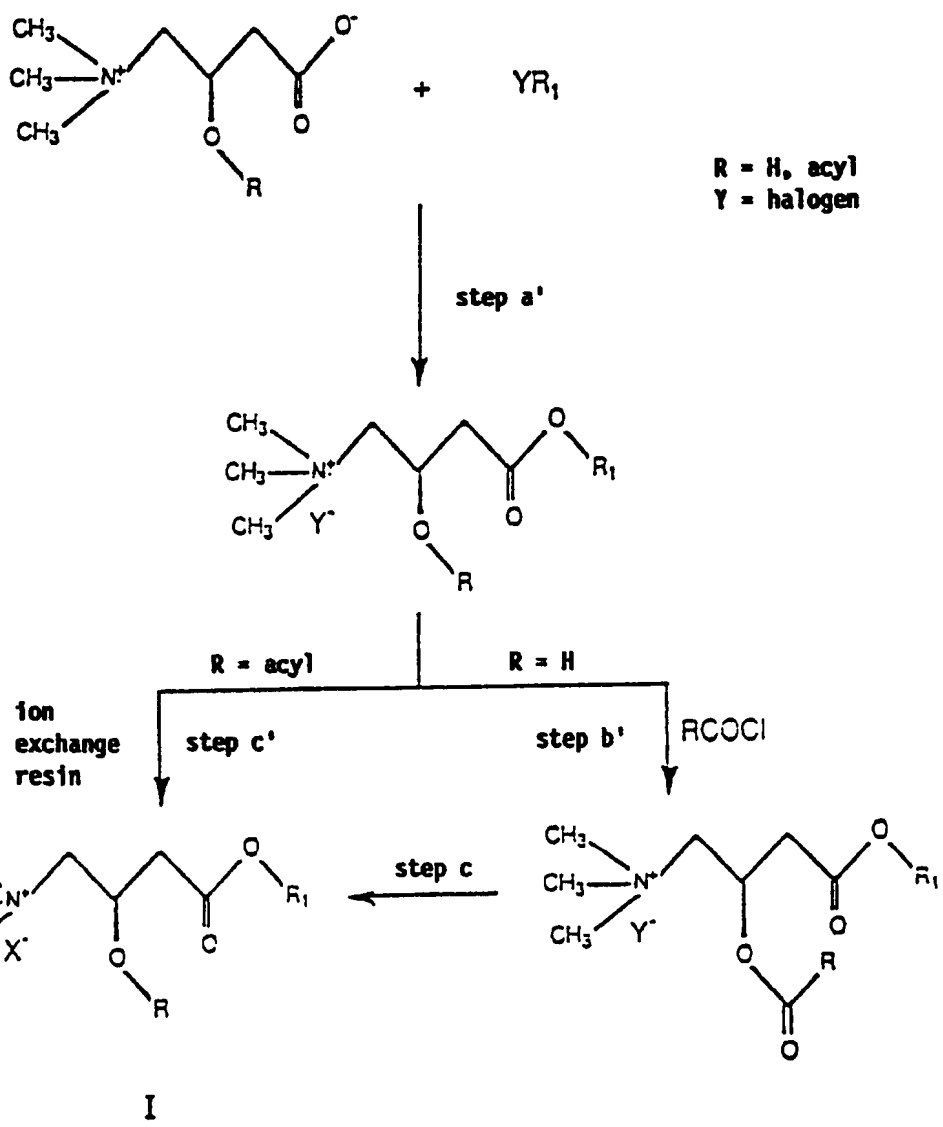
8-24 hours and then isolating the resulting compound by concentration;
(b') acylating the ester obtained in step (a') with the desired acid chloride by known techniques, in case the starting compound in step (a') is carnitine;
(c') eluting an aqueous or alcoholic solution of the compound of step (a') or (b') on an ion exchange resin such as Amberlite IRA 402 or Amberlist A 21 activated with the desired HX acid.

Synthesis Scheme 1



R = acyl

Synthesis Scheme 2



I

Example 1

Preparation of acetyl L-carnitine heptyl ester chloride (ST 904)

Step (a'): Preparation of acetyl L-carnitine heptyl ester iodide.

Acetyl L-carnitine inner salt (30 g; 0.148 moles) was suspended in 50 ml anhydrous CH_3CN. To this mixture heptyl iodide (24.5 ml; 0.149 moles) was added. The resulting solution was reacted for 12 hours at 50 °C and then concentrated under vacuum. An oily residue was obtained which was used as such in the next step.

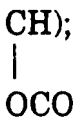
Step (c'):

The raw products of step a' was dissolved in H_2O and eluted through a column of 600 ml Amberlite IRA 402 resin activated in Cl^- form. The collected eluate was lyophilized and 45 g of a vitreous solid product were obtained. Yield 91%.

$[\alpha]^{25}_D$ = -11.2(c = 0.5% $CHCl_3$)
E.A. $C_{16}H_{32}ClNO_4$

	C%	H%	N%	Cl%
calculated (anhydrous)	56.96	9.49	4.15	10.52
found	54.63	10.17	4.06	9.74

H_2O 3.8%
HPLC
Column: Spherisorb Cl 5 μm
t: 50 °C
Flow rate: 1 ml/min
Rt: 17.44 min
NMR D_2O δ 5.6 (1H,m,



4.1 (2H,t,OCH_2); 4.0-3.7 (2H,m,N + CH_2-); 3.3 (9H,s,$(CH_3)_3N^+$); 2.8 (2H,dd,CH_2COO); 2.1 (3H,s,$COCH_3$); 1.3 (10H,m, $(CH_2)_5$); 0.9 (3H,m,CH_2CH_3)

Example 2

Preparation of isobutyryl L-carnitine heptyl ester chloride (ST 713)

Step (a): Preparation of the acid chloride of isobutyryl L-carnitine chloride.

Isobutyryl L-carnitine chloride was suspended in oxalyl chloride (16 ml; 0.095 moles). The mixture was kept under stirring at room temperature for 6 hours. Anhydrous ethyl ether was then added till complete precipitation of an oily product. The solution was concentrated and the residue washed three times with anhydrous acetone and dried under vacuum. 9 g of product were obtained. The raw product was used as such in the next step.

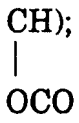
Step (b): Preparation of isobutyryl L-carnitine heptyl ester chloride (ST 713).

To the acid chloride of isobutyryl L-carnitine (9 g) (prepared as shown in step a), heptanol (50 ml) was added under stirring at 0 °C.

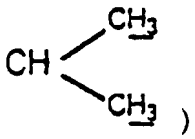
The resulting solution was kept at room temperature for 8 hours, then concentrated under vacuum to a small volume, diluted with $CHCl_3$ and chromatographed on silica buffered with 2% Na_2HPO_4. The column was eluted with $CHCl_3$ to remove the unreacted heptanol and then against $CHCl_3$-MeOH gradient till 100% MeOH. The oily residue thus obtained was repeatedly washed with hexane and dried under vacuum.
10.5 g of a hygroscopic oily product were obtained. Yield 89%.
TLC $CHCl_3$-MeOH-H_2O-IsoprOH (60-40-15-10)
RF = 0.7
$[\alpha]^{25}_D$ = -16.7 (c = 1% H_2O)
E.A. $C_{18}H_{36}NO_4Cl$

	C%	H%	N%	Cl%
calculated (anhydrous)	59.07	9.91	3.82	9.68
found	56.87	10.30	3.63	9.12

H_2O 4.6%
HPLC
Column: Lichrosorb BRP2 (10 μm)
Mobile phase: $(NH_4)_2HPO_4$ 0.05M-CH_3CN (1:1)
pH 7 with H_3PO_4
Flow rate: 2 ml/min
RT = 7.44
RT = 5.07 10% carnitine heptil ester
NMR $CDCl_3$ δ 5.5 (1H,m,

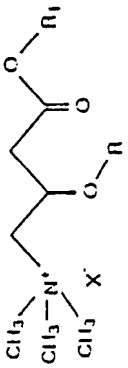


4.2-3.8 (4H,m,N^+CH_2-; OCH_2); 3.3 (9H,s, $(CH_3)_3N^+$); 2.7 (2H,m,CH_2COO); 2.4 (1H,m,COCH); 1.5-0.8 (19H,m, $(CH_2)_5$-CH_3;



The compounds of Examples 3-7 were prepared following the procedures disclosed in Example 1.

The compounds of Examples 8-9 and 12-32 were prepared following the procedures disclosed in Example 2.



Ex.	ST code R	R_1	HPLC RI	H_2O% KF	E.A. C%	H%	N%	Cl%	$[\alpha]_D^{25}$ c = 1% H_2O	NMR δ $CDCl_3$
3	ST 665 isobutyryl	n-butyl	4,04[a]	3%	calc. 55,63 9,33 4,32 10,95 found 53,36 9,36 4,17 10,60				- 19,3	5,7(1H,m,CH); 4,2-4,0(4H,m,N^+CH_2;OCH_2); 3,3 (9H,s,$(CH_3)_3N^+$); 2,9(2H,m,CH_2COO); 2,5 (1H,m,OCOCH); 1,6 (2H m,$CH_2CH_2CH_2CH_3$); 1,4 (2H,m,$CH_2CH_2CH_3$); 1,1 (6H,d,$CH(CH_3)_2$);0,9 (3H,m,CH_2CH_3)
4	ST 305 isobutyryl	iso-butyl	5,65[b]	3,6%	calc. 55,80 9,36 4,33 10,67 found 50,28 9,72 4,28 10,99				-19,5	5,7(1H,m,CH); 4,0-3,8(4H,m,N^+CH_2; OCH_2); 3,2 (9H,s,$(CH_3)_3N^+$); 2,9(2H,m,CH_2COO); 2,6 (1H,m,COCH); 2,0 (1H m,$CH(CH_3)_2$); 1,2 (6H,d,$CH(CH_3)_2$); 0,9 (6H,d,$CH(CH_3)_2$)

Ex.	ST code R	R_1	HPLC Rt	H_2O% KF	E.A.	C%	H%	N%	Cl%	$[\alpha]_D^{25}$ c = 1% H_2O	NMR δ $CDCl_3$
5	ST 683 **iso-valeryl**	**n-butyl**	6,44[a]	0,5%	**calc.** 55,28 9,83 4,29 10,87 **found** 55,29 9,68 4,06 19,7					-18,7	5,7(1H,m,CH(OCO)); 4,4-4,0(4H,m,N^+CH_2; OCH_2); 3,5 (9H,s,$(CH_3)_3N^+$); 2,8(2H,m,CH_2COO); 2,2 (2H,m,$COCH_2$); 2,1 (1H m,CH(CH3)2); 1,6(2H,m,$CH_2CH_2CH_3$); 1,4 (2H,m,CH_2,CH_3); 0,9(9H,m,CH(CH3)2 ;CH_2CH_3)
6	ST 684 **iso-valeryl**	**iso-butyl**	7,66[b]	1,8%	**calc.** 56,88 9,55 4,15 10,49 **found** 55,80 9,61 5,44 10,42					-18	5,7(1H,m,CH(OCO)); 4,0-3,6(4H,m,OCH_2;N^+CH_2); 3,2 (9H,s,$(CH_3)_3N^+$); 2,8(2H,m,CH_2COO); 2,4 (1H,m,COCH2); 2,0(2H m,2CH(CH3)2); 0,9(12H,dd, 2CH(CH3)2)

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Ex.	ST code n	R_1	HPLC Rt	H_2O% KF	E.A.				$[\alpha]_D^{25}$ c = 1% H_2O	NMR δ $CDCl_3$
						C%	H%	N%	Cl%	
7	ST 697	heptyl isovaleryl	8,77[d]	2,2%	calc.	60,05	10,67	3,68	9,34	- 15[f]	5,7(1H,m,CH); 4,2-3,8(4H,m,N^+CH_2; OCH_2); 3,2 (9H,s,$(CH_3)_3N^+$); 2,8(2H,d,CH_2COO) 2,2 (2H,m,$OCOCH_2CH$); 1,5 (1H m,CH); 1,2 (13H, m,$(CH_2)_5CH_3$); 0,9 (6H,d,CH)
					found	56,61	10,34	3,29	9,24		
8	ST 895 H	heptyl	8,91[e]	2,5%	calc.	56,83	10,22	4,74	11,98	-10,6	4,6(1H,m,CH); 4,1(2H,l,$COOCH_2$); 3,6 (2H,m,N^+CH_2); 3,2(9H,s,$(CH_3)_3N^+$); 2,8 (2H,m,CH_2COO), 1,6 (2H,m,OCH_2CH_2);1,3 (8H,s,$(CH_2)_4$) 0,9(3H,l,CH_3)
					found	55,40	10,23	4,62	11,68		
9	ST 951	hexacosyl acetyl	/	0,7%	calc.	69,07	11,87	2,30	5,82	-10,4[g]	5,7 (1H,m,CH); 4,4-4,0 (4H,dm,$\overset{+}{N}CH_2$; OCH_2); 3,5 (9H,s,$(CH_3)_3\overset{+}{N}$) 2,9(2H,m,CH_2COO); 2,2 (3H,s,$COCH_3$); 1,6(2H,m,CH_2);1,3 (46H,s,$(CH_2)_{23}$); 0,9(3H,s,CH_3)
					found	68,74	12,62	2,33	5,65		

a: Lichrosorb RP_2 (10 µ) column, t=35°C, eluant CH_3CN-50mM KH_2PO_4 (30-70), flow rate 1 ml/min

b: Delta PAK C_4 (15 µm) column, eluant CH_3CN-50mM KH_2PO_4 (35-65), flow rate 1 ml/min

c: Spherisorb C_1 (4.6 mm) column, eluant CH_3CN-50mM KH_2PO_4 (50-50), flow rate 1 ml/min

d: as c, eluant CH_3OH-50mM KH_2PO_4 (60-40)

e: as c, eluant CH_3CN-KH_2PO_4 (30-70)

f: c=1% MeOH

g: c=1% $CHCl_3$

Example 10

Preparation of isovaleryl L-carnitine undecyl ester chloride (ST 722)

Step A: Preparation of isovaleryl L-carnitine chloride acid chloride.

Isovaleryl L-carnitine chloride (30 g; 0.106 moles) was suspended in 100 ml anhydrous CH_2Cl_2.

The mixture was cooled at 0 °C and oxalyl chloride (13 ml; 0.15 moles) diluted in 15 ml anhydrous CH_2Cl_2 was slowly added under stirring.

After 30 minutes at room temperature, a further amount of oxalyl chloride (19 ml; 0.21 moles) diluted in 10 ml anhydrous CH_2Cl_2 was added.

The resulting solution was kept under stirring for 2 hours at room temperature, then concentrated under vacuum.

The residue thus obtained was washed twice with anhydrous CH_2Cl_2 and concentrated under vacuum.

The raw products thus obtained was used as such in the next reaction.

Step B: Preparation of isovaleryl L-carnitine undecyl ester chloride (ST 722).

The acid chloride previously prepared (0.106 moles) was dissolved in anhydrous CH_2Cl_2 (40 ml).

The solution was cooled at 0 °C and undecylic acid (35 ml; 0.168 moles) diluted in 35 ml CH_2Cl_2 was added in a nitrogen atmosphere.

The solution was kept under stirring at room temperature for 2 hours and then concentrated under vacuum until an oily residue was obtained.

The raw reaction mixture was chromatographed on a silica gel column buffered with 2% Na_2HPO_4, eluting with CH_2Cl_2 till complete elution of undecylic alcohol and then with CH_2Cl_2-MeOH 9:1 till complete elution of the compound.

The pooled fractions were concentrated and gave 28 g of the title compound; yield 60%.

$[\alpha]^{25}_D$ = -10.5 (c = 1% H_2O)

E A. $C_{23}H_{46}ClNO_4$

	C%	H%	N%	Cl%
calculated (anhydrous)	63.35	10.63	3.21	8.13
found	60.87	0.88	3.29	8.14

H_2O 2.4%

HPLC

Column: Spherisorb Cl (5 μm)

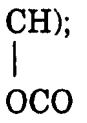
t: 50 °C

Eluant: CH_3OH/50 mM KH_2PO_4 (65:35)

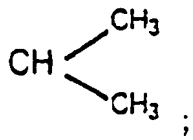
Flow rate: 1 ml/min

RT = 14.82 min

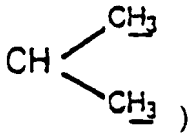
NMR $CDCl_3$ δ 5.5 (1H,m,



4.2-3.8 (4H,m,N + CH_2-; OCH_2); 3.3 (9H,s, $(CH_3)_3N^+$); 2.8(2H,m,CH_2COO); 2.2(2H,m,$OCOCH_2$); 1.6-1.0 (22H,m,



$(CH_2)_9$-CH_3); 0.8 (6H,d,



Example 11

Preparation of isobutyryl L-carnitine undecyl ester chloride (ST 712)

The compound was prepared as described in Example 10, substituting isobutyryl L-carnitine chloride for isovaleryl L-carnitine chloride. Yield 55%.

$[\alpha]^{25}_D$ = -15.8 (c = 1% H_2O)

E.A. $C_{22}H_{44}O_4NCl$

	C%	H%	N%	Cl%
calculated (anhydrous)	62.61	10.51	3.32	8.40
found	61.77	10.67	3.29	8.17

H_2O 0.8%

HPLC

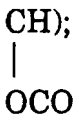
Column: Spherisorb CI (4.6 μm)

Eluant: CH_3OH/50 mM KH_2PO_4 (60:40)

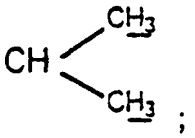
Flow rate: 1 ml/min

RT = 14.75 min

NMR $CDCl_3$ δ 5.5 (1H,m,



4.2-3.8 (4H,m,N^+CH_2-; OCH_2); 3.3 (9H,s, $(CH_3)_3N^+$); 2.8 (2H,m,CH_2COO); 2.5 (1H,m,COCH); 1.5-0.9 (27H,m,



$(CH_2)_9$-CH_3)

Ex code	R	n	X^-	[α] 25 D	E.A. found C	H	N	Cl	H_2O	m.p. °C	HPLC Rt min	NMR δ
12 ST 1034	isocaproyl	10	Cl^-	-13,12 (c=0,8% H_2O)	$C_{24}H_{48}NO_4Cl$ 61,28%	11,10%	3,12%	9,01%	1,9%	oil /not determined	8,45[d]	5,7(1H,m,CHO);4,1(2H,t,OCH_2);4,0-3,7(2H,m, CH_2N^+); 3,2(9H,s,$(CH_3)_3N^+$); 3,0-2,7(2H,m,CH_2COO); 2,6-2,3(2H,m, $OCOCH_2$); 1,7-1,4(5H,m,$2CH_2$,-CH); 1,3 (16H, broad,$8CH_2$); 0,9 (6H,d, $(CH_3)_2$); 0,8(3H,t,CH_3). D_2O
13 ST 1036	eptanoyl	10	Cl^-	-12,1 (c=1% H_2O)	$C_{25}H_{49}NO_4Cl$ 64,35%	12,55%	3,09%	6,68%	1,3%	not determined	9,35[d]	5,7(1H,m,CHO); 4,1(2H,t,OCH_2); 4,0-3,7 (2H,m,CH_2N^+); 3,2 (9H,s,$(CH_3)_3N^+$); 3,0-2,7 (2H,m,CH_2COO); 2,5-2,3(2H,m, $COCH_2$); 1,6(4H,m,$2CH_2$); 1,3(22H,m, $11CH_2$); 0,9-0,8(6H,2t,$2CH_3$). D_2O
14 ST 1050	eptanoyl	12	Cl^-	-10,3 (c=0,7% $CHCl_3$)	$C_{27}H_{54}NO_4Cl$ 65,26%	11,62%	2,87%	6,70%	0,3%	dec. 150-160	9,13[e]	5,7(1H,m,CHO); 4,3-4,0 (4H,m,CH_2N^+; OCH_2); 3,5 (9H,s,$(CH_3)_3N^+$); 2,8(2H,m, CH_2COO); 2,3(2H,m,$OCOCH_2$); 1,6(4H, m,$2CH_2$); 1,3(26H,m,$13CH_2$); 0,9(6H,2t, $2CH_3$). $CDCl_3$
15 ST 1051	2-methyl esanoyl	12	Cl^-	-8,8 (c=1% $CHCl_3$)	$C_{27}H_{54}NO_4Cl$ 65,06%	11,32%	2,91%	6,93%	0,4%	not determined	28,03[b]	5,7(1H,m,CHO); 4,3-4,0 (4H,m,CH_2N^+; OCH_2); 3,5 (9H,s,$(CH_3)_3N^+$); 2,8(2H,m, CH_2COO); 2,4 (1H,m,CH); 1,6(2H,m, CH_2);1,3(26H,m,13 CH_2);1,1 (3H,m, $CHCH_3$);0,9(6H,2t,$2CH_3$). $CDCl_3$
16 ST 1033	isovaleryl	12	Cl^-	-11,8 (c=1%H_2O)	$C_{25}H_{50}NO_4Cl$ 63,73%	12,50%	3,17%	7,03%	1,2%	dec. 150	9,39[d]	5,7(1H,m,CHO);4,1(2H,m,OCH_2);4,0-3,7 (2H,m,CH_2N^+);3,2(9H,s,$(CH_3)_3N^+$);3,0-2,7(2H,m,CH_2COO);2,3(2H,m,$OCOCH_2$); 2,1(1H,m,CH_2CH);1,6(2H,m,CH_2);1,3 (20H, broad, 11 CH_2);0,9 (6H,dd, $CH(CH_3)2$);0,8(3H,t,CH_3). D_2O

Ex code	R	n	X⁻	[α]25 D	E.A. found					m.p. °C	HPLC Rt min	NMR δ
					C	H	N	Cl	H_2O			
17 ST 1052	esanoyl	12	Cl^-	-10,7 (c=1%$CHCl_3$)	$C_{26}H_{52}NO_4Cl$ 65,01%	11,87%	2,93%	7,14%	1,2%	dec. 120-130	14,86[c]	5,7(1H,m,CHO);4,3-4,0(4H,m, CH_2N^+;OCH_2); 3,5(9H,s,$(CH_3)_3N^+$); 2,9-2,7(2H,m,CH_2COO); 2,3(2H,t,$OCOCH_2$); 1,6(4H,m,$2CH_2$); 1,3(24H, broad,12 CH_2); 0,9(6H,m,$2CH_3$). $CDCl_3$
18 ST 1053	octanoyl	12	Cl^-	-9,8 (c=1%$CHCl_3$)	$C_{28}H_{56}NO_4Cl$ 66,46%	11,93%	2,71%	6,93%	0,7%	dec. 150-160	14,71[c]	5,7(1H,m,CHO);4,3-4,0(4H,m, CH_2N^+;OCH_2); 3,5(9H,s,$(CH_3)_3N^+$); 2,9-2,7(2H,m,CH_2COO); 2,3(2H,m,$OCOCH_2$); 1,6(4H,m,$2CH_2$); 1,3(28H, broad,14 CH_2); 0,9(6H,m,$2CH_3$). $CDCl_3$
19 ST 1037	isovaleryl	11	Cl^-	-12,2 (c=1%H_2O)	$C_{24}H_{48}NO_4Cl$ 63,46%	12,26%	3,15%	7,81%	1,0%	dec. 150-160	12,65[a]	5,7(1H,m,CHO);4,4-4,0(4H,m, N^+CH_2; OCH_2) 3,5(9H,s,$N^+(CH_3)_3$); 2,8(2H,m,CH_2COO); 2,2(2H,m,$OCOCH_2$); 2,0(1H,m,$CH(CH_3)_2$); 1,6 (2H,m,CH_2); 1,2(18H,broad, 9CH_2); 0,9-0,8(9H,d+t, CH_3;$(CH_3)_2$). $CDCl_3$
20 ST 1038	isobutirryl	11	Cl^-	-14,5 (c=1%H_2O)	$C_{23}H_{46}NO_4Cl$ 62,90%	11,47%	3,27%	7,86%	0,4%	dec. 150-155	14,0[a]	5,7(1H,m,CHO);4,4-4,0(4H,m, N^+CH_2; OCH_2); 3,5(9H,s,$N^+(CH_3)_3$); 2,9-2,7(2H,m,CH_2COO);2,6-2,5(1H,m, $CH(CH_3)_2$);1,6(2H,m,CH_2);1,3(18H, broad, 9CH_2); 1,1 (6H,d, $CH(CH_3)_2$); 0,8 (3H,t,CH_3). $CDCl_3$
21 ST 1060	eptanoyl	11	Cl^-	-12,7 (c=1%MeiOH)	$C_{26}H_{52}NO_4Cl$ 67,00%	12,12%	2,41%	6,60%	0,6%	not determined	10,47[f]	5,7(1H,m,CHO);4,4-4,0(4H,m, N^+CH_2; OCH_2); 3,5(9H,s,$N^+(CH_3)_3$); 2,8(2H,m,CH_2COO);2,4(2H,t, $COOCH_2$) 1,6(2H,m,CH_2);1,3 (26H, broad ,13 CH_2); 0,9 (6H,2t, $2CH_3$)

Ex code	R	n	X⁻	[α]25 D	E.A. found C	H	N	Cl	H_2O	m.p. °C	HPLC Rt min	NMR δ
22 ST 1018	isovaleryl	10	tartrate acid	-1,9 (c=1%H_2O)	$C_{27}H_{51}NO_{10}$ 56,87%	9,78%	2,44%		4%	not determined	13,74[a]	5,7(1H,m,CHO);4,5(2H,s, 2CHOH); 4,1-3,6 (4H,m, N^+CH_2; OCH_2); 3,2 (9H,s,$N^+(CH_3)_3$); 3,0-2,7(2H,m,CH_2COO); 2,4-2,2(2H,m, $OCOCH_2$); 2,1-2,0 (1H, m, CH(CH_3)2);1,6(2H,m,CH_2);1,3 (16H, broad, 8CH_2); 0,9(6H,d,CH(CH_3)2); 0,8(3H,t,CH_3). D_2O
23 ST 1017	isovaleryl	10	fumarate acid	- 13,3% (c=1%H_2O)	$C_{27}H_{49}NO_8$ 62,23%	9,90%	2,54%		0,7%	dec. 120	13,99[a]	6,6(2H,s,CH=CH); 5,7(1H,m,CHO); 4,1-3,7(4H,m,N^+CH_2;OCH_2);3,2(9H,s,$N^+(CH_3)_3$); 3,0-2,7(2H,m,CH_2COO);2,4-2,2 (2H,m,$OCOCH_2$);2,0(1H,m,CH(CH_3)2); 1,6(2H,m,CH_2);1,3(16H,broad,8CH_2);0,9 (6H,t,CH(CH_3)2);0,8(3H,t,CH_3). D_2O
24 ST 1035	isovaleryl	6-undecil	Cl^-	-12,9 (c=1%H_2O)	$C_{23}H_{46}NO_4Cl$ 61,33%	10,81%	3,27%	6,69%	1,3%	dec. 150-160	7,39[f]	5,7(2H,m,CHO);4,8(1H,q,CH);4,4-4,0 (2H,m,N^+CH_2);3,4(9H,s,$N^+(CH_3)_3$); 2,8(2H,m,CH_2COO);2,2(2H,m, $OCOCH_2$);2,1(1H,m,CH(CH_3)2);1,5(4H, m,2CH_2);1,3(6H,broad,3CH_2); 1,0-0,9(9H,d+t,CH(CH_3)2;CH_3).$CDCl_3$
25 ST 1013	H	10	Cl^-	- 11,2% (c=0,7%H_2O)	$C_{18}H_{38}NO_3Cl$ 59,85%	11,72%	3,87%	9,45%	1,4%	oil not determined	11,90[a]	4,7 (1H,m,CHOH); 4,1(2H,m,$COOCH_2$); 3,5-3,4(2H,m,N^+CH_2);3,3(9H,s, $(CH_3)_3N^+$);2,6(2H,m,CH_2COO); 1,7(2H,m,CH_2);1,3(16H,m,8CH_2); 0,9(3H,t,CH_3). D_2O

Ex code	R	n	X⁻	[α]25 D	E.A. found C	H	N	Cl	H_2O	m.p. °C	HPLC Rt min	NMR δ
26 ST 1014	isovaleryl	$CH_2CH=CH_2$	Cl^-	- 11,1% (c=1%$CHCl_3$)	$C_{23}H_{44}NO_4Cl$ 61,43%	10,66%	3,14%	7,40%	1,5%	oil not determ.	14,92[a]	6,0-5,8(1H,m,C<u>H</u> =CH_2);5,7(1H,m, CHOCO);5,1-5,0(2H,m,CH=C<u>H</u>$_2$); 4,2(2H,t,$COOCH_2$);4,0-3,8(2H,m,N^+CH_2) 3,3(9H,s,$(CH_3)_3N^+$);2,9(2H,m,CH_2COO); 2,3(2H,d,$OCOCH_2$);2,2-2,0(3H,m,CH_2; C<u>H</u>$(CH_3)_2$);1,7(2H,m,CH_2);1,4(14H, broad,7CH_2);1,0(6H,d,2CH_3).CD_3OD
27 ST 1015	isovaleryl	$CH_2CH=CH_2$	fumarate acid	- 11,8% (c=1%H_2O)	$C_{27}H_{47}NO_8$ 62,07%	9,39%	2,66%		0,8%	oil not determ.	10,42[e]	6,8(2H,s,CH =CH);6,0-5,8(1H,m, C<u>H</u> =CH_2);5,7(1H,m,CHOCO); 5,1-5,0(2H,m,CH=C<u>H</u>$_2$);4,2(2H,t, $COOCH_2$);4,0-3,8(2H,m,N^+CH_2) 3,3(9H,s,$(CH_3)_3N^+$);2,9(2H,m,CH_2COO); 2,3(2H,d,$OCOCH_2$);2,2-2,0(3H,m,CH_2; C<u>H</u>$(CH_3)_2$);1,7(2H,m,CH_2);1,4(14H, broad,7CH_2);1,0(6H,d,2CH_3).CD_3OD
28 ST 1016	isovaleryl	$CH_2CH=CH_2$	tartrate acid	- 2,7% (c=1%H_2O)	$C_{27}H_{51}NO_{10}$ 58,08%	9,45%	2,51%		0,9%	oil not determ.	11,33[a]	6,0-5,8(1H,m,C<u>H</u> =CH_2);5,7(1H,m, CHOCO);5,1-5,0(2H,m,CH=C<u>H</u>$_2$); 4,4(2H,s,2C<u>H</u>OH);4,2(2H,t,$COOCH_2$);4,0 -3,8(2H,m,N^+CH_2);3,3(9H,s, $(CH_3)_3N^+$);2,9(2H,m,CH_2COO); 2,3(2H,d,$OCOCH_2$);2,2-2,0(3H,m,CH_2; C<u>H</u>$(CH_3)_2$);1,7(2H,m,CH_2);1,4(14H, broad,7CH_2);1,0(6H,d,2CH_3).D_2O
29 ST 1032	isovaleryl	7	Cl^-	- 17,4% (c=1%H_2O)	$C_{20}H_{40}ClNO_4$ 59,98%	11,66%	3,55%	8,64%	1,7%	oil not determ.	5,75[f]	5,7(1H,m,C<u>H</u>OCO);4,1(2H,m,$COOCH_2$); 4,0-3,7(2H,m,N^+CH_2);3,2(9H,s, $(CH_3)_3N^+$);3,0-2,7(2H,m,CH_2COO); 2,3(2H,m,$OCOCH_2$);2,1(1H,m,C<u>H</u> $(CH_3)_2$);1,6(2H,m,CH_2);1,3(10H,broad; 5CH_2);1,0(6H,d,$CH(C\underline{H}_3)_2$); 0,8(3H,t,CH_3). D_2O

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Ex code	R	n	X⁻	[α]25 D	E.A. found C	H	N	Cl	H_2O	m.p. °C	HPLC Rt min	NMR δ
30 ST 1055	stearoyl	10	Cl^-	- 2,7% (c=1%$CHCl_3$)	$C_{36}H_{72}NO_4Cl$ 68,21%	12,05%	2,14%	5,72%	1,9%	oil not determ.	17,89[g]	5,7(1H,m,CHOCO);4,4-4,0(4H,m,N^+CH_2; $COOCH_2$);3,4(9H,s,$(CH_3)_3N^+$);2,8(2H,m, CH_2COO);2,3(2H,m,$OCOCH_2$);1,7(20H, broad,$10CH_2$);1,3(28H,broad,$14CH_2$); 0,9(3H,t,CH_3).$CDCl_3$
31 ST 1072	isovaleryl	9	Cl^-	- 13,6% (c=1%H_2O)	$C_{22}H_{44}NO_4Cl$ 58,88%	8,24%	3,17%	7,53%	1%	oil not determ.	6,11[e]	5,7(1H,m,CHOCO);4,1(2H,m,$COOCH_2$); 4,0-3,8(2H,m,N^+CH_2);3,2(9H,s, $(CH_3)_3N^+$);3,0-2,7(2H,m,CH_2COO); 2,4(2H,m,$OCOCH_2$);2,1(1H,m,CH $(CH_3)_2$);1,7(2H,m,CH_2);1,3(14H,broad, $7CH_2$);1,0(6H,d,$CH(CH_3)_2$);0,9(3H,t, CH_3)D_2O
32 ST 1048	10-undecenoyl	$CH_2=CH-CH_2$	Cl^-	- 6,4% (c=1%$CHCl_3$)	$C_{29}H_{54}NO_4Cl$ 66,80%	11,15%	2,61%	7,01%	0,6%	oil not determ.	25,22[h]	5,9-5,8(2H,m,$2CH=CH_2$); 5,6(1H,m,CHOCO);5,0(4H,m,$2CH=CH_2$); 4,4-4,0(4H,m,N^+CH_2;$COOCH_2$); 3,4(9H,s,$(CH_3)_3N^+$);2,8(2H,m,CH_2COO); 2,4(2H,t,$OCOCH_2$);2,0(4H,m,$2CH_2$-CH=) 1,6(4H,broad,$2CH_2$);1,4-1,2(20H,broad, $10CH_2$).$CDCl_3$

Ex code	R	n	X⁻	[α]25 D	E.A. found C	H	N	Cl	H2O	m.p. °C	HPLC Rt min	NMR δ
33 ST 1000	octanoyl	10	Cl⁻	-10,7 (c=1%CHCl3)	$C_{26}H_{52}NO_4Cl$ 62,84%	10,7%	3,03%	6,96%	3,2%	103-105	10,28[a]	5,7(1H,m,CHO);4,3-4,0 (4H,m,CH2N⁺; OCH2); 3,5(9H,s,(CH3)3N⁺); 2,8 (2H,m, CH2COO); 2,3(2H,t,OCOCH2);1,8(4H,m, 2 CH2); 1,6 (4H,m;2 CH2); 1,3 (20H, broad, 10 CH2); 0,9 (6H, 2t, 2 CH3).CDCl3
34 ST 1001	isovaleryl	15	Cl⁻	-12,6 (c=0,5%H2O)	$C_{28}H_{56}NO_4Cl$ 65,30%	11,11%	2,68%	7,57%	0,5%	not determined	12,12[a]	5,7(1H,m,CHO);4,4-4,0(4H,m, N⁺CH2; OCH2); 3,5(9H,s,N⁺(CH3)3); 2,8(2H,m,CH2COO);2,2(3H,m, CH(CH3)2);1,6(2H,m,CH2);1,3(26H, broad, 13 CH2);1,0-0,9(9H,d+t, CH3,CH(CH3)2). CDCl3
35 ST 1061	Hexacosanoyl	3	Cl⁻	-12,6 (c=0,5%H2O)	$C_{37}H_{74}NO_4Cl$ 69,46%	12,37%	2,38%	5,20%	1,3%	not determined	not determined	5,7(1H,m,CHOCO);4,4-4,0(4H,m, N⁺CH2; COOCH2); 3,3(9H,s,(CH3)3N⁺); 2,8(2H,m,CH2COO);2,4(2H,m, OCOCH2);2,2 (1H,broad,CH2);1,64H,m, 2CH2);1,2-1,1(44H,broad,22CH2),1,0-0,9(6H,d+t,2CH3). CDCl3

a: Column: Nucleosil-SA (5 μ) 1.2 mm, i.d. 4.0 mm
t: 40°C
Mobile phase: 50mM $(NH_4)_2HPO_4/CH_3CN$ 1:1 pH 4 with H_3PO_4
Flow rate: 0.75 ml/min

b: Column: Spherisorb C1 (5 μ) 1.2 mm, i.d. 4.6 mm
t: 50°C
Mobile phase: CH_3OH/50mM KH_2PO_4 60:40
Flow rate: 0.5 ml/min

c: Column: Spherisorb C1 (5 μ) 1.2 mm, i.d. 4.6 mm
t: 50°C
Mobile phase: CH_3OH/50mM KH_2PO_4 70:30 pH 3.9 with H_3PO_4
Flow rate: 0.5 ml/min

d: Column: Spherisorb C1 (5 μ) 1.2 mm, i.d. 4.6 mm
t: 40°C
Mobile phase: CH_3OH/50mM KH_2PO_4 65:35 pH 4.5 with H_3PO_4
Flow rate: 0.5 ml/min

e: Column: Nucleosil-SA (5 μ) 1.2 mm, i.d. 4.0 mm
t: 30°C
Mobile phase: 50mM $(NH_4)_2HPO_4/CH_3CN$ 65:35 pH 3.5 with H_3PO_4
Flow rate: 0.75 ml/min

f: Column: Spherisorb C1 (5 μ) 1.2 mm, i.d. 4.6 mm
t: 40°C
Mobile phase: CH_3OH/50mM KH_2PO_4 65:35 pH 4.5 with H_3PO_4
Flow rate: 1 ml/min

g: Column: Spherisorb C1 (5 μ) 1.2 mm, i.d. 4.6 mm
t: 50°C
Mobile phase: CH_3CN/50mM KH_2PO_4 70:30
Flow rate: 0.8 ml/min

h: Column: Spherisorb C1 (5 μ) 1.2 mm, i.d. 4.6 mm
t: 50°C
Mobile phase: CH_3CN/50mM KH_2PO_4 60:40
Flow rate: 1 ml/min

Binding studies of ca^{++} channel receptors

The "binding" of the tested compounds to the sites associated to calcium channels labeled by ^3H-Nitrendipine, ^3H-Verapamil and ^3H-Diltiazem has been assayed in rat brain according to the method of

Schoemaker H. et al. Eur. J. Pharmacol. 111, 273 (1985) and of Reynolds I.J. et al. Eur. J. Pharmacol. 95, 319 (1983).

Brain cortices are removed from decollated male Crl: CD (SD) BR rats weighing 250-300 g.

The tissues were homogenized in Tris-HCl buffer and centrifuged at 50000 x g for 10 minutes. The pellet was washed twice through a fresh buffer suspension and centrifuged at 50000 x g for 10 minutes.

After suspension of the precipitate in the incubation buffer the compounds under examination were added to the medium, starting from a concentration 10^{-5} M. Incubation conditions were: ^{3}H-Nitrendipine (0.5 nM) x 60' at 30 °C; ^{3}H-Verapamil (10 μM) x 20' at 37 °C; and ^{3}H-d-cis Diltiazem (4 nM) x 60' at 30 °C. Final volume was 1 ml. Incubation was stopped by rapid filtration under vacuum through GF/B (0.1% polyethylene) fiber filters which were washed with cold incubation buffer (3 x 3 ml) using the system of filtration Brandel Cell Harvester. Filters were put in 8 ml of Optifluor (Packard) and the radioactivity bound to the membranes trapped by fibers counted by liquid scintillation spectrometer TRI-CARB 1900 CA (Packard). The counting efficiency was about 50%.

Evaluation of binding data

The percentage inhibition of the specific ^{3}H-ligand binding to its respective receptors was calculated for each concentration (mean of three incubates).

The competition curve, the slope of the curve and IC_{50} ± standard deviation values (drug concentration that reduces specific ^{3}H-ligand binding to its respective receptors by 50% of its maximum value) were calculated by using the "Allfit" program (De Lean A. et al., Am. J. Physiol. 235, E97, 1978) running on an IBM 55-SH. The results obtained are shown in Table 1. Compounds resulted inactive at the concentration 10^{-5} M have not been tested at higher concentrations.

Assessment of behaviour and mortality in mice

The assessment of normal behaviour in mice was carried out following S. Irwin's method, Psychopharmacologia 13, 222 (1968). This method allows alterations in some behavioural, neurophysiologic and neurovegetative parameters to be detected, which are directly observable by the researcher. The study was conducted using male Crl: (CD-I)(ICR)BR mice (Charles River - Italy) weighing 22-25 g, following oral administration of the compounds suspended in carboxymethylcellulose (0.5% by weight in H_2O) to groups of 4 animals/dose.

The animals were continuously kept under observation for five hours following treatment and twice a day in the subsequent five days. Mortality was also observed during the overall test period. The initial dose was 1000 mg/kg per os; lower doses were administered in case of death or if the initial dose brought about an excessive response.

The results are shown in Table 2.

ST 722 studies on isolated organs

The compound was examined in the following preparations of isolated organs:

- Guinea pig ileum
- Rat portal vein

Isolated guinea pig ileum

Antagonism to Ca^{++} induced contractions

ST 722 action has been tested in ileal segments K^+ depolarized and bathed in Ca-free physiological solution at 37 °C. A contractile response was evoked by $CaCl_2$ as described by Spedding M., J. Pharmac. 83, 211 (1984). ST 722 antagonized dose-dependently from 0.1 to 1 μg/ml $CaCl_2$ contractions.

Antagonism to angiotensin induced contractions

Ileal segments bathed at 37 °C wered made to contract by angiotensin according to the method of Rubin B. et al., J. Pharmacol. Exper. Therap. 204, 271 (1978). ST 722 dose-dependently inhibited angiotensin effect in dose ranging from 0.1 to 1 μg/ml.

Antagonism to substance P induced contractions

Inhibition to the submaximal contractile response evoked by substance P has been determined in ileum segments bathed at 37 °C as described by Holtzer P. et al., Eur. Pharm. 91, 83 (1983). Doses ranging from 0.1 to 1 µg/ml resulted active.

Antagonsim to methacholine contractions

The compound action has been assayed by using ileum segments made to contract by methacholine chloride according to Magnus R. et al., Physiol. 102, 123 (1904). ST 722 antagonized dose-dependently from 0.1 to 1 µg/ml methacholine contractions.

Rat portal vein

The effect of the compound on the contractions evoked by high K^+ concentrations in the rat portal vein has been tested according to Shetty S.S. et al., Europ. J. Pharm. 141, 485 (1989). ST 722 resulted inactive at a concentration of 10 mg/ml.

Study of the effect on blood pressure and heart rate

The effect of the substance has been tested after oral administration of 100 mg/kg to conscious spontaneously hypertensive rats (SHR). No changes of blood pressure and heart rate were observed 1, 2 and 4 hours after the administration. The experimental procedure was run according to Yeer T.T. et al, Life Sciences 22, 359 (1978).

In conclusion, compounds of the invention resulted active in inhibiting the binding to sites associated to Ca^{++} channels at concentrations of pharmacological interest.

The compounds of the invention, like reference Ca-antagonists, antagonize the contractile activiti of the ileum, but at variance with reference compounds are inactive on contractile activity of portal vein. In addition, they counteracted the contractions evoked by angiotensin, substance P and methacholine.

A pharmacological profile such as shown by these compounds, a Ca-antagonist and anti-cholinergic action in the gastrointestinal tract , but not in other districts (see rat portal vein) in absence of effects on blood pressure "in vivo" is absolutely unexpected.

Table 1

Compound	IC_{50} Uptake sites of Ca^{++} channels labelled with		
	^{3}H-Nitrendipine	^{3}H-Verapamil	^{3}H-Diltiazem
ST 305	3.3×10^{-5}	3.5×10^{-6}	$> 10^{-5}$
ST 683	$> 10^{-5}$	2.4×10^{-6}	1.5×10^{-5}
ST 684	$> 10^{-5}$	1.6×10^{-6}	7.8×10^{-6}
ST 697	$> 10^{-5}$	1.5×10^{-6}	5×10^{-7}
ST 712	5.3×10^{-6}	2.8×10^{-6}	1.2×10^{-6}
ST 713	$> 10^{-5}$	1.2×10^{-6}	1.3×10^{-6}
ST 722	1.6×10^{-6}	3.8×10^{-7}	1.4×10^{-6}
ST 904	$> 10^{-5}$	3.2×10^{-6}	$> 10^{-5}$

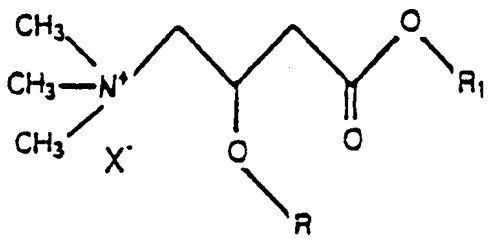
Table 2

Assessment of behaviour and death rate in mice			
Compound	Dose	Symptoms	Death rate
ST 305	1000	n.e.	0/4
ST 683	300	n.e.	0/4
	600	convulsions (*)	2/4
	1000	convulsions (*)	4/4
ST 684	1000	n.e.	0/4
ST 697	100	n.e.	0/4
	300	convulsions (*)	1/4
	600	convulsions (*)	2/4
	1000	convulsions (*)	4/4
ST 712	1000	n.e.	0/4
ST 713	100	n.e.	0/4
	300	convulsions (*)	2/4
	600	convulsions (*)	3/4
	1000	convulsions (*)	4/4
ST 722	1000	salivation, diarrhea	0/4
ST 895	300	n.e.	0/4
	600	convulsions (*)	2/4
	1000	convulsions (*)	4/4
ST 904	300	n.e.	0/4
	600	convulsions (*)	2/4
	1000	convulsions (*)	4/4
n.e. = no effect			

(*) = in connection with death rate only

Claims

1. Esters of L-carnitine and acyl L-carnitine of formula (I):



(I)

wherein
R is hydrogen or is a straight or branched, saturated or unsaturated acyl group having 2 to 26 carbon atoms;
R_1 is a straight or branched, saturated or unsaturated alkyl group having 4 to 26 carbon atoms; and
X^- is the anion of a pharmacologically acceptable acid.

2. Esters according to claim 1, wherein R is

(a) a saturated straight acyl group selected from acetyl, propionyl, butyryl, palmitoyl, undecanoyl and hexacosanoyl; or
(b) a branched acyl group selected from isobutyryl, isovaleryl, isocaproyl and 2-methylheaxanoyl; or
(c) 10-undecenoyl.

3. Esters according to claims 1 or 2, wherein R_1 is
(a) a saturated straight alkyl group selected from n-butyl, n-heptyl, n-undecyl and n-hexacosyl; or
(b) a branched alkyl group selected from isobutyl, isooctyl, hexylmethylcarbyl, ethylpentylcarbyl, ethylhexylcarbyl, decylmethylcarbyl, dipentylcarbyl and methylnonylcarbyl; or
(c) an unsaturated alkyl group selected from pentylvinylcarbyl and 10-undecenoyl.

4. Esters according to anyone of the preceding claims, wherein X^- is selected from chloride; bromide; iodide; aspartate, particularly acid aspartate; citrate, particularly acid citrate; tartrate; phosphate, particularly acid phosphate; fumarate, particularly acid fumarate; glycerophosphate; glucosephosphate; lactate; maleate, particularly acid maleate; orotate; oxalate, particularly acid oxalate; sulphate, particularly acid sulphate; trichloroacetate; trifluoroacetate and methansulphonate.

5. Acetyl L-carnitine heptyl ester chloride.

6. Isobutyryl L-carnitine heptyl ester chloride.

7. Isobutyryl L-carnitine n-butyl ester chloride.

8. Isobutyryl L-carnitine isobutyl ester chloride.

9. Isovaleryl L-carnitine n-butyl ester chloride.

10. Isovaleryl L-carnitine isobutyl ester chloride.

11. Isovaleryl L-carnitine heptyl ester chloride.

12. L-carnitine heptyl ester chloride.

13. Acetyl L-carnitine hexacosyl ester chloride.

14. Isovaleryl L-carnitine undecyl ester chloride.

15. Isobutyryl L-carnitine undecyl ester chloride.

16. An orally or parenterally administrable pharmaceutical composition comprising an ester of anyone of the preceding claims as active ingredient and a pharmacologically acceptable excipient therefor.

17. The composition of claim 16 having muscle relaxant activity selective on the gastrointestinal tract.

18. The composition of claim 16 for treating adaptive colitis syndromes and pathological conditions characterized by increased intestinal contractility and/or motility.